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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,354	HARIRI ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,27,28 and 31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, 27, 28, and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/2/08 and 12/2/08 has been entered.

2. Claims 1-13, 27, 28, and 31-36 are all the pending claims for this application.

3. Claims 1, 13, 34 and 35 were amended in the Response of 10/2/08 and 12/2/08.

4. Claims 1-13, 27, 28, and 31-36 are all the pending claims under examination.

Withdrawal of Objections

Claim Objections

5. The objection to Claims 1 and 13 for misspelling “angiogensis” is withdrawn in view of the amended claims in the Response of 10/2/08.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

6. The rejection of Claims 13 and 32 because the relationship between the plurality of tumor cells and the microvessel outgrowth from the vessel section is unclear is

withdrawn. The amendment of Claim 13 in the Response of 10/2/08 to define the relationship between the microvessel and the tumor cells obviates the rejection.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. The rejection of Claim 13 under 35 U.S.C. 102(e) as being anticipated by Drake et al. (WO 01/63281; published 8/30/01; priority to 2/23/00; cited in the IDS of 10/4/07) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 12/5/07 as follows:

"Drake discloses a method for screening an agent (agonist or antagonist) that promotes or inhibits angiogenesis or vasculogenesis comprising culturing embryonic, allantoic or mesodermal (mesenchymal) stem cells with the agent, and detecting an increase in endothelial cells in the culture compared to a control culture, where the increase indicates that the agent promotes vasculogenesis and a decrease in endothelial cells indicates an agent that inhibits vasculogenesis (pp. 3, line 13- p. 4, line 6). Drake teaches that allantoic cells or an ex vivo culture of allantois that includes mesodermal stem cells (mesenchymal) and endothelial cells can be used to screen for factors that affect angiogenesis and/or vasculogenesis (p. 3, line 7-9). Drake discloses that the method also allows for the detection of the formation of vasculature or vascular remodeling (p. 4, lines 22-23) such as the formation of vascular networks (p. 10, lines 20-21). Drake teaches that the method substrate can include bone-marrow derived stem cells or allantois, explant, organ, tissue, graft or tumor, and adding the test agent to the culture medium (p. 12, lines 28-29). Drake teaches de novo vessel formation by vasculogenesis are overlooked using screening methods with only endothelial cells because endothelial cells can only be used to measure angiogenesis where allantoic mesodermal stem cells allows observation of vasculogenesis (p. 8, line 24-29). Drake teaches that the agent and cells should "be cultured for 1-48 hours, but the time can vary depending on the half life of the agent and could be optimized by one skilled in the art using routine experimentation" (p. 13, line 6-10) or culturing in medium "for weeks or months" (p. 12, line 23). Drake discloses that an agent that promotes or inhibits vasculogenesis or angiogenesis would be an agent that would also slow or prevent tumor growth (p. 15, lines 11-22). Drake teaches a GelFoam sponge assay composed of collagen type I (p. 37, line 34- p. 38, line 5) for growing endothelial stem precursors and soaking the

sponges in the angiogenesis stimulator, VEGF (Example 9) or treating allantois with VEGF, bFGF and HGF (Example 5). Drake teaches assays using human breast carcinoma cell lines (Example 10).

The rejection was maintained in the Office Action of 6/2/08 as follows:

"Claim 13 is interpreted as being drawn to a method for identifying a modulator of angiogenesis comprising culturing a vessel section in the presence of a plurality of tumor cells and a test compound under conditions that enable microvessel outgrowth from the section and comparing microvessel outgrowth from the vessel between the test and a control sample.

Applicants' allegations on the top of p. 8 of the Response of 3/5/08 have been considered but are not found persuasive. Applicants allege that Drake does not disclose the use of tumor cells in the assays as presently claimed, and that Example 10 in Drake is a prophetic example directed only to an assay to determine the effect of tumor cells on angiogenesis and vasculogenesis in an irradiated mouse.

The examiner submits that Drake discloses methods for assessing the potency of a candidate agent that promotes or inhibits neovascularization. For example, potency of an agent can be determined by measuring tumor growth; an amount that slows or prevents tumor growth would be a therapeutically effective amount of an agent that inhibits neovascularization (p. 15, lines 17-20); Drake explains that the methods for screening for angiogenesis would involve contacting a substrate such as a culture or organ or tumor with the agent, where the agent is added to the culture medium (i.e., "by changing the medium to a medium that contains the agent") or by adding the agent to the extracellular fluid in vivo (p. 12, lines 25-32). Thus implicit to Drakes disclosure is the fundamental understanding that a tumor would contain microvessels, which when contacted by the test agent, would either stimulate or inhibit microvessel outgrowth, thus effecting tumor growth. Drake further teaches in the same paragraph that vasculature can be imaged using techniques known in the art, including, for example, angiography (fluorescein angiography, radio-angiography, or indocyanine grene angiography). Further, Example 10 of Drake is provided as an example of an in vivo model for examining angiogenesis in breast tumors and on which the screening methods for test agents could be readily practiced in vivo. Drakes' disclosure encompasses explanted tissues from tumors that would contain a vessel(s) and a plurality of tumor cells and thus the disclosure of Drake is maintained as reading on the method of Claim 13."

Applicants allegations on pp. 7 of the Response of 10/2/08 have been considered and are not found persuasive. Applicants allege that in order to distinguish the instant method from Drake, Claim 13 is amended to be an *in vitro* method, whereas Drake teaches a hypothetical in vivo method in Example 10; and Claim 13 requires microvessel outgrowth from a vessel ring whereas Drake fails to teach the same.

Response to Arguments

Initially, the examiner resubmits that Drake teaches performing in vitro methods such as where Drake states:

"the methods for screening for angiogenesis would involve contacting a substrate such as a culture or organ or tumor with the agent, *where the agent is added to the*

culture medium (i.e., "by changing the medium to a medium that contains the agent") (p. 12, lines 25-32); and

"The contacting step can be either in vivo, ex vivo, or *in vitro*" (p. 14, line 23).

Second and contrary to Applicants assertion, Claim 13 does not recite that "a vessel ring" is cultured in vitro. The claims recites a "vessel section" with a plurality of tumor cells and would encompass any section of vessel or an explanted vascularized tumor tissue or organ, or any tissue or organ undergoing tumorigenesis comprising some aspect of a vessel section by virtue of its dissection and being explanted. The instant specification defines a "vessel section" as "a cross-section that appears to be ring-shaped, but *may be any section of vessel* that is culturable. The vessel may be any vessel (i.e., arterial, venous, lymphatic, etc.)" (at p. 8, lines 25-27).

The rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The rejection of Claims 1, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drake et al. (WO 01/63281; published 8/30/01; priority to 2/23/00; cited in the IDS of 10/4/07) in view of Zygmunt (Early Pregnancy 5(1):72-73 (Jan 2001)) is maintained.

For purposes of review, the rejection from the Office Action of 12/5/07 is set forth as follows:

"The claimed method was prima facie obvious over Drake and Zygmunt.

The interpretation of Drake is discussed supra. Drake discloses using allantoic explants in assaying for stem cell differentiation into endothelial cell precursors for formation of vessels structures and various other organs but does not disclose using placental-derived stem cells as endothelial cell precursors, which does Zygmunt.

Zygmunt discloses that placental vascularization occurs by vasculogenesis and angiogenesis and is mediated by endothelial progenitor cells present in the developing primitive organ. Zygmunt does not describe the phenotype of the placental stem cells for endothelial progenitors, but one of skill in the art would envisage that the endogenous placental stem cells inherently possess the phenotype of CD34- (Claim 26), or Oct-4+, SSEA3- and SSEA4- (Claim 27) or CD10+, CD29+, CD44+, Cd54+, CD90+, SH2+, SH3+ SH4+, OCT4+, CD34-, CD38-, CD45-, SSEA3- and SSEA4- (Claim 28), where the markers were already known in the art and the technology (PCR primers for detecting the respective mRNA or antibodies specific for each cell marker for FACS sorting) for separating cells with the phenotype was well within the ordinary skill of the artisan at the time of the invention. ("The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997)).

One skilled in the art would have been motivated and reasonably assured of success in having produced the method for identifying a modulator of angiogenesis using placental-derived stem cells comprising endothelial progenitors based on the combined disclosures of Drake and Zygmunt. Drake discloses the culture conditions for assaying angiogenesis modulators (agonist and antagonist) which effect allantoic-derived stem cell differentiation into endothelial cells and Zygmunt discloses that placenta also contains endothelial progenitor stem cells critical for forming blood vessels. One skilled in the art could have readily modified the culture conditions of Drake by introducing the placental-derived stem cells disclosed in Zygmunt and having the inherent phenotype and/or selecting for a phenotype of CD34-, *or* Oct-4+, SSEA3- and SSEA4-, *or* CD10+, CD29+, CD44+, Cd54+, CD90+, SH2+, SH3+ SH4+, OCT4+, CD34-, CD38-, CD45-, SSEA3- and SSEA4- because Zygmunt discloses that the placenta is rich in endothelial cell progenitors capable of forming vessel beds. One skilled in the art would have been reasonably assured of success in having introduced the placental-derived stem cells into the culture assay system of Drake because the stem cells were recognized as being endogenous cells known to be essential for differentiation into microvessels."

The rejection was maintained in the Office Action of 6/2/08 as follows:

Applicants' allegations on pp. 10-11 of the Response of 3/5/08 have been considered but are not found persuasive. Applicants allege that the Examiner has not cited any reference authority to support the inherency rejection that Zygmunt's placental precursor cells would be inherently CD34- much less that the placental precursors would have the phenotype for Oct-4+, SSEA3- and SSEA4- (Claim 27) or CD10+, CD29+, CD44+, Cd54+, CD90+, SH2+, SH3+ SH4+, OCT4+, CD34-, CD38-, CD45-, SSEA3- and SSEA4- (Claim 28). Applicants further allege that the angioblasts of Zygmunt would be CD34+ as evidenced by Urbich and Dimmler (Circulation Res. 95:343-353 (2004)), where at p. 344, Col. 1, Urbich teaches "that angioblasts and hemangioblasts" are CD34+.

The examiner respectfully submits that the Urbich reference supplied by Applicants supports and substantiates the examiner's original position that precursor cells with a CD34- phenotype would give rise to endothelial progenitor cells. Urbich specifically teaches "There is increasing evidence that myeloid cells can give rise to endothelial cells as well. Specifically, CD14+/CD34- myeloid cells can co-express endothelial markers and form tube-like structures ex vivo" (p. 344, Col. 1, ¶3). Thus contrary to Applicants assertion, a precursor or stem cell having the CD34- phenotype was known in the art to give rise to endothelial cells. Thus absent a showing to the contrary, a CD34- stem cell further having the phenotype for Oct-4+, SSEA3- and SSEA4- or CD10+, CD29+, CD44+, Cd54+, CD90+, SH2+, SH3+ SH4+, OCT4+, CD38-, CD45-, SSEA3- and SSEA4- would have been inherent to the placental precursors described by Zygmunt.

Applicants' allegations on pp. 8-9 of the Response of 10/2/08 have been considered and are not found persuasive. Applicants allege "the rejection still has not established that the endothelial progenitor cells mentioned in--but not described--by Zygmunt are the recited placental stem cells, which are CD34-, for the reasons already of record. The present rejection does not contest that Urbich, Circulation Res. 95:343-353 (2004) teaches that angioblasts (endothelial progenitor cells) are CD34+. As such, Urbich demonstrates that Zygmunt teaches away from the claimed invention. The rejection provides no reason why a person of ordinary skill in the art would believe the recited placental stem cells to be myeloid cells. Moreover, the rejection still has provided no basis for asserting that the cells mentioned in Zygmunt are each of OCT-4+, SSEA-3- and SSEA-4-, as recited in claim 27, or each of CD10+, CD29+, CD34-, CD38-, CD44+, CD45-, CD54+, CD90+, SH2+, SH3+, SH4+, OCT-4+, SSEA-3- and SSEA-4-, as recited in claim 28. Again, the rejection must provide a rationale or evidence tending to show inherency. MPEP, Section 2100 at page 2100-47. The rejection must also show that the

Response to Arguments

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley , 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. Gillette Co. v.

S.C. Johnson & Son, Inc., 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness. Here in contrast to applicant's assertions that Urbich demonstrates that Zygmunt teaches away from the claimed invention; there is no discouragement or skepticism found in Urbich that teaches away from endothelial precursors giving rise to vasogenesis as taught by Zygumnt. On the contrary, Urbich teaches a CD34- progenitor cell (myeloid) gives rise to a "tube-like structure" (p. 344, Col. 1, ¶3). Urbich teaches that the same progenitor cells express endothelial markers and are incorporated into newly formed blood vessels in vivo. Urbich teaches that the CD34- precursor can differentiate or transdifferentiate to endothelial lineage.

The claimed CD34- stem cell appears to be the same as the prior art precursors involved in angiogenesis or vasogenesis and which form tube-like structures, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989)."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

9. The rejection of Claims 1-12, 27, 28, 31, and 33-36 under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for just any method of scoring formation of "tube-like structures" from the CD34- stem cells per se in the presence of any test compound.

For purposes of review, the rejection was set forth in the Office Action of 6/2/08 as follows:

> "Nature of the Invention/ Skill in the Art
> Claims 1-12, 27, 28, 31, and 33-36 are broadly drawn to a method for identifying a modulator of angiogenesis or vasogenesis in a method comprising culturing a plurality of isolated human CD34- placental stem cells under conditions in which microvessel outgrowth from the placental stem cells occurs and where an amount of microvessel outgrowth from the stem cells in the presence of the modulator is compared to a control amount of microvessel outgrowth. The claims are interpreted as the CD34- placental stem cells per se being able to actually produce or differentiate into microvessels.
> The relative skill in the art required to practice the invention is a clinical technician with a background in cell culture and microscopy.
> Disclosure in the Specification/ Undue Experimentation/ Unpredictability
> The specification does not disclose that the CD34- placental stem cells isolated from human placenta drained of cord blood and perfused to remove residual blood, and placed under any culture conditions in vitro, would per se give rise to or produce microvessels. The specification discloses the following examples using the CD34- placental stem cells or human umbilical vessel sections and the results observed from those studies:
> Example 6.1/6.2 (working): the stem cells were cultured alone in vitro and shown to develop tube-like structures and to express different markers. Addition of modulators effected expression of different markers (Table 2) and the branching or bifurcation of the cells (Table 4);
> Example 6.3.2 (working): human umbilical cord vessel rings were cultured in the presence of modulators to compare microvessel outgrowth (Table 6);
> Example 6.4 (prophetic): vessel rings and stem cells are co-cultured in the presence of modulators and examined for angiogenesis vis-à-vis vessel outgrowth; and
> Example 6.5 (prophetic): vessel rings and tumor cells are co-cultured in the presence of modulators.
> Significantly, no where in the specification have applicants demonstrated that the CD34- placental stem cells would actually produce or differentiate into microvessels. The closest demonstration of a structural change is the tube formation in Example 6.1 and the branching form in Example 6.2.
> According to Urbich et al. (Circulation Res. 95:343-353 (2004)) the ordinary artisan could only predict that CD14+/CD34- myeloid cells can co-express endothelial markers and form tube-like structures ex vivo" (p. 344, Col. 1, ¶3).
> Thus Applicants own specificaiton is not enabling for its explicit or implicit disclosure for the isolation conditions or the culture conditions that would allow microvessel outgrowth to occur from the stem cells in vitro. The

ordinary artisan must be able to discriminate between the effect of the test compound on microvessel outgrowth and the general ability of the stem cells to differentiate into or produce the microvessels in vitro. The conditions that allow microvessel outgrowth from the stem cells to occur is seemingly critical and even rate limiting insofar as achieving the method endpoint, namely, identifying a modulator of angiogenesis or vasogenesis based on the outgrowth of microvessels from the stem cells. It is unpredictable that the ordinary artisan could even culture the CD34- stem cells and expect to observe microvessel outgrowth occurring from the cells themselves. The ordinary artisan would be required to perform undue trial and error experimentation to identify the culture conditions that would permit microvessel outgrowth for the isolated stem population to occur based on the written description of the specification alone."

Applicants allegations on pp. 10-11 of the Response of 10/2/08 have been considered and are not found persuasive. Applicants allege that in amending the claims to recite that the placental stem cells form tube-like structures, that the results from Example 2, p. 64, Table 2 and Example 1, section 6.2.2, Table 4 and Figure 3 are proof of enablement for use of the isolated cells *per se* in the assay method.

Response to Arguments

No where in the specification do Applicants define a "tube-like structure" much less the culture conditions permissive for in vitro differentiation of any "isolated placental CD34- stem cell" to differentiate into this structure. It is not even clear what morphological or phenotypic characteristics comprise a "tube-like structure" since no such structure was contemplated at the time of the invention.

The specification states:

"As used herein, the term "vasogenesis" refers to generation or formation of tubes or microtubules" (p. 8, lines 23-24);

"Spontaneous vasogenesis may be characterized by the assembly of microtubular structures. In this method, test compounds are assayed for their ability to modulate the assembly of these microtubule structures" (p. 11, lines 31-32); and

"Human pluripotent stem cells were plated immediately upon isolation and adherent cells were selected from non-adherent populations after 24 hours. These adherent cells were cultivated in DMEM supplemented with 10% cord blood serum (CBS) and antibiotics. The time course profile of spontaneous vasogenesis, as characterized by assembly of *microtubular structures*, was determined and cell specimens and collected

at various time points to assay for endothelial specific markers and synthetic products" (6.1; p. 58).

The culture conditions provided in the specification for measuring microtubular or tubular structures was based on a starting population of embryonic-like human placental stem cells characterized by the presence of the following cell surface markers: CD 10, CD29, CD44, CD54, CD 90, SH2, SH3, SH4, OCT-4 and ABC-p, and the absence of the following cell surface markers: CD34, CD38, CD45, SSEA3 and SSEA4 (p. 47, lines 15-18).

It is not clear that just any CD34- cell obtained from the placenta would have the inherent property of differentiating into a tube or microtubular structure associated with angiogenesis or vasogenesis. It is not clear that the ordinary artisan could practice the instant claimed method if the only feature and requirement of the starting cell population is that it is a CD34- placental stem cell. For example, what other stem cells in the human placenta are CD34- and do can they all differentiate into tubes or microtubules? The prior art is dispositive to any assumption that just any isolated human CD34- placental stem cell could form "tube-like structures" much less tubes, microtubules or tubular structures associated with angiogenesis or vasogenesis.

Zhang et al. (Clin. Med. J. 117:882-887 (2004); Abstract) teach that a population of placental derived mesenchymal stem cells exhibiting fibroblastoid morphology and having the phenotype CD29+, Cd44+, CD73+, CD105+, CD166+, HLA-ABC+, CD34-, CD45-, and HLA-DR- could be induced into adipocytes or osteocytes.

Zhang et al. (Exp. Hematol. 32:657-664 (2004); Abstract) teach that a placental derived mesenchymal progenitor displaying fibroblastoid morphology and having the phenotype CD73+, CD105+, CD29+, CD44+, HLA-ABC+, CD166+, CD14-, CD31-, CD34-, CD45-, HLA-DR- and alpha-smooth muscle actin-, and producing laminin, fibronectin and vimentin, could be induced into adipocytes, osteocytes and chondrocytes.

Chen et al. (Stem Cells 26:550-561 (2008)) teaches that a population of maternal stem cells that traffic through the placenta are Lin-, CD34- and contribute to maternal microchimerism in the fetus.

Portmann-Lanz et al. (Am. J. Obstetrics & Gyn. 194:664-673 (2006)) teaches MSCs isolated from placenta have the phenotype CD166+, CD105+, Cd90-, CD73+, CD49e+, CD44+, CD29+, Cd13+, MHC I+, CD14-, CD34-, CD45-, MHC II- were able to differentiate into mesodermal cells consistent with mature chondroblasts, osteoblasts, adipocytes or myocytes and neuronal cells.

The ordinary artisan could not reasonably expect to practice the method with any degree of predictability using just any CD34- stem cell isolated from the human placenta, and expect to identify modulators of angiogenesis or vasogenesis vis-à-vis the formation of tubes, tubules or tubular structures, based on the prior art knowledge of placental CD34- stem cells and their pluripotency, e.g., ability to differentiate into different kinds of tissues and organs depending on their phenotypic markers and the specific growth conditions in vitro. The rejection is maintained.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Partial Signatory Authority